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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/034,213	01/03/2002	Anthony T. Maurelli	04995.0044-01	7868

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EXAMINER
GRASER, JENNIFER E

ART UNIT	PAPER NUMBER
1645	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/034,213	Applicant(s) Maurelli et al.
	Examiner Jennifer Graser	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Jan 3, 2002, Prel. Amendt A*

2a)☐ This action is **FINAL.** 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18)☐ Interview Summary (PTO-413) Paper No(s). _____

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other:

DETAILED ACTION

Specification

1. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Original claim 3 mentions the use of putrescine in the pharmaceutical composition; however, no mention of putrescine was found in the specification.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to pharmaceutical compositions for the treatment or prophylaxis of (*any)* gastrointestinal disorders comprising (*any*) diaminoalkyl compound and a pharmaceutically acceptable carrier. Claim 4 teaches that the gastrointestinal disorders result from an infection by a wide range of bacteria, including *Y.pestis, M.tuberculosis, N.gonorrhoeae, Listeria,* etc. Methods for preventing gastrointestinal orders using the pharmaceutical compositions are also claimed.

First, diaminoalkyl compounds encompass a huge class of different compounds. The success of one diaminoalkyl group in treating or preventing a gastrointestinal disorder does not directly correlate to a different diaminoalkyl compound's success in the same method. For example, Wang (US 5,502,055) teaches that while the diaminoalkyl compound, putrescine, was shown to exhibit a protective effect against endotoxic shock which is caused by the LPS molecule, endotoxin, contained in the cell wall of all gram-negative bacteria, spermine showed no protective effect against endotoxin shock (see column 1, lines 45-49 and col. 1, lines 12-15). The specification provides no experiments with diaminoalkyl groups other than cadaverine. Accordingly, the claims are not enabled for the use of any pharmaceutical composition comprising any diaminoalkyl compounds, other than cadaverine, or methods of using said compound to treat or prevent a gastrointestinal order. Further, with respect to cadaverine, the specification has not enabled the use of this compound to treat or prevent *any* gastrointestinal disorder. The instant specification provides no results of experiments which demonstrate cadaverine's ability to treat or prevent gastrointestinal disorders. The specification teaches that cadaverine when applied *in vitro* for thirty minutes to intestinal epithelium or PMNs could attenuate the toxic effect of *Shigella*.. However, this does not demonstrate the prevention of *any* gastrointestinal disorder in a human or in an animal, nor does it enable the treatment of gastrointestinal disorders resulting from an infection by any of the bacterium recited in claim 4. There are no *in vivo* treatment experiments provided which demonstrate that cadaverine when administered to a subject could treat or prevent a gastrointestinal disorder. Further, the

experiments in the specification required pretreatment of cells for 30 minutes with cadaverine in order to achieve some treatment result. A pharmaceutical compound administered to a live subject would not have this reaction time. The experiments provided do not correlate to how the composition would act *in vivo*. Additionally, in order to obtain coverage for "prophylaxis or prevention" challenge experiments of animals are required. The vaccine art is highly unpredictable. Applicants should provide further evidences which directly show the treatment of gastrointestinal disorder and/or prevention if they wish to obtain the scope of the current claims.

The prior art also teaches that polyamines, such as cadaverine and putrescine, are a potential hazard to human health because of their effects on aminopeptidase activity (Yolanda et al. J.Food Science, 1997, 62(4): p. 870 abstract). They are also taught to be toxic in certain levels an a potential cause of food poisoning (Ordonez et al. J. Food Protection, 1997, 60(11): 1371, abstract). Certain amines, including putrescine and cadaverine, are implicated in certain central nervous system diseases, such as migraine, Parkinson disease, epilepsy and depressive illness (Gabastou et al. Pathologie Biolgie, 1996. 44(4), p. 275, abstract). The specification does not provide the amount of cadaverine or other diaminoalkyl group which would be sufficient to treat or prevent a gastrointestinal order in a host without causing a more detrimental effect.

Lastly, gastrointestinal disorders arise from a multitude of different causes ranging from ulcers to cancers, spicy foods to bacterial infection, and gas to the use of antibiotics or analgesics to viral infection, for example. The prior teaches that it is highly unpredictable for one substance to provide relief from or prevent gastrointestinal disorders stemming from all of these different

origins. Claims 1-3 and 5-7 do not limit the gastrointestinal disorder to a particular origin. Further, Claim 4 recites bacteria from several different Genus, many of which are not known to cause gastrointestinal disorders. Further, many of these bacterium are well known in the art to have no known preventative cure, i.e., *M.tuberculosis.* The specification does not enable treatment or prevention from disorders caused by these many different bacterium, nor does it enable treatment or prevention of any gastrointestinal disorder. The information provided in the instant specification which does not provide any practical examples is not sufficient to enable the scope of the instant claims

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

In the instant case, (1) the nature of the invention is the treatment or prophylaxis of a gastrointestinal disorder through the use of any diaminoalkyl compound. (2) The state of the prior art is silent as to the use of a diaminoalkyl compound in the prevention of gastrointestinal disorders. Additionally, the state of the prior art with regard to treating and, especially, preventing gastrointestinal disorder is (3) highly unpredictable. Gastrointestinal disorders arise

from a multitude of different causes ranging from ulcers to cancers, spicy foods to bacterial infection, and gas to the use of antibiotics or analgesics to viral infection, for example. Further, the prior teaches that it is highly unpredictable for one substance to provide relief from or prevent gastrointestinal disorders stemming from all of these different origins. The information provided in the instant specification which does not provide any practical examples is not sufficient to enable the scope of the instant claims. (4) There is no direction or guidance presented for treating or preventing gastrointestinal disorders or for the amount of cadaverine (or other diaminoalkyl compound) which when administered to a mammal, particularly a human, could prevent all future gastrointestinal disorders. (5) There are also no working examples relating to the prevention or treatment of gastrointestinal disorders through the administration of a diaminoalkyl compound present in the instant specification. (6) Accordingly, the quantity of experimentation necessary is undue (7) even though the relative skill of those in the art is high. (8) The specification does not enable the breadth of the instant claims. The specification fails to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 3, 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang (US 5,502,055).

Wang teaches a pharmaceutical composition comprising an effective amount of putrescine and a pharmaceutically acceptable carrier. Methods for protecting a living subject from endotoxin shock by administering said pharmaceutical composition are also disclosed. See abstract. Wang teaches that while the diaminoalkyl compound, spermine showed no protective effect against endotoxin shock, putrescine did exhibit a protective effect against endotoxic shock which is caused by the LPS molecule, endotoxin, contained in the cell wall of all gram-negative bacteria (see column 1, lines 45-49 and col. 1, lines 12-15). Endotoxic shock is known to cause hypotension and signs of poor tissue perfusion (col. 1, lines 13-16). Endotoxic shock falls under a 'gastrointestinal disorder'. The endotoxic shock studied by Wang was caused by *E.coli*. See Example in Column 2.

6. Claims 1, 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Keusch et al (Biochem. Biophys. Res. Comm.1984, 121(1): 69-76).

Keusch et al teach that putrescine could inhibit translocation of shigella toxin from the cell surface to the cytosol (abstract). It is disclosed that putrescine inhibited cytotoxicity to some degree and was able to afford some protection to HeLa cells in in vitro experiments (p. 71). Keusch teach that primary amines, including putrescine, could inhibit the cytotoxic action of shigella toxin and/or permit antibody rescue of the intoxicated cells long after this becomes impossible in the absence of the amines (p. 74, first full paragraph). Claims 1, 3 and 4 are

product claims. The phrase "pharmaceutical composition for the treatment or prophylaxis of gastrointestinal disorders " and "wherein the gastrointestinal disorders result from an infection selected from the group consisting of...." are intended uses only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, the it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the compounds used in the reference.

7. Claims 1, 2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Dela Vega et al (The Euro Journal. 1995 vol. 14(23): 6059-65).

DelaVega et al teach that cadaverine induces the closing of *E.coli* porins (see abstract). The reference teaches that inhibitors of channel porins are of great value in the design of therapeutic agents (p. 6059, col. 1, bottom of first paragraph). The reference teaches that their finding of porin inhibition by cadaverine opens the way to investigating a series of compounds with inhibitory properties (p. 6059, col. 1, bottom of first paragraph). Claims 1, 2 and 4 are product claims. The phrases "pharmaceutical composition", "for the treatment or prophylaxis of gastrointestinal disorders", "wherein the gastrointestinal disorders result from an infection selected from the group consisting of....", and "wherein the gastrointestinal disorders result from an infection by *Shigella* spp.", are intended uses only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the

prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, the it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the compounds used in the reference. The composition of the prior art and the claimed compositions are structurally identical and therefore the teachings of Dela Vega et al are anticipatory on the composition claims.

8. Claims 1, 2 , 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Dela Vega et al (J.Baceriol., July 1996, 178(13): 3715-3721).

DelaVega et al teach that cadaverine and putrescine induce the closing of bacterial porins (see abstract). It is disclosed that both OmpC and OmpF porins ere inhibited (abstract). The references teaches that four diaminoalkyl compounds, putrescine, cadaverine, spermidine, and spermine, were able to inhibit fluxes of B-lactam antibiotics in live cells and chemotaxin (abstract). The reference teaches that polyamines may act as endogenous modulators of outer membrane permeability (abstract). Claims 1-4 are product claims. The phrases "pharmaceutical composition", "for the treatment or prophylaxis of gastrointestinal disorders", "wherein the gastrointestinal disorders result from an infection selected from the group consisting of....", and "wherein the gastrointestinal disorders result from an infection by *Shigella* spp.", are intended uses only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the

intended use, the it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the compounds used in the reference. The composition of the prior art and the claimed compositions are structurally identical and therefore the teachings of Dela Vega et al are anticipatory on the composition claims.

Status of claims

9. No claims are allowed. Putrescine and cadaverine were both well known and isolated compounds at the time the invention was made as evidenced by the prior art set forth above. Accordingly, these products combined with solely a pharmaceutically acceptable carrier, which reads on water, are not novel. However, new methods of using these molecules, provided there is enablement and written description for these methods, may be allowable.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1641 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Graser

JENNIFER E. GRASER
PRIMARY EXAMINER

2/12/03